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(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

The invention relates to an inhalant pharmaceutical composition or air scenting composition comprising a volatile active ingredient-cyclodextrin inclusion complex and a competitor host molecule as well as conventionally used excipients.

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PHARMACEUTICAL COMPOSITION

The present invention relates to a pharmaceutical inhalant composition and a process to release the volatile active ingredients included to cyclodextrin.

During pharmaceutical treatments it is often necessary to get volatile active ingredients, volatile oils to the organism especially in case of the deseases of the respiratory organs (bronchitis, laryngitis, rhinitis, tracheitis etc). The preferred way to get the volatile active ingredients into the respiratory tract is by inhalation and the volatile active ingredients are preferably used in the form of inhalant compositions. The inhalant composition is a pharmaceutical composition which contains the vapour of the active ingredients or liquid drops of various size dispersed in the air. The inhalant composition can have various forms: a natural source such as dried plant drug can be boiled in hot water or it can be extracted and ampouled and it has to be put in hot water after opening the ampoule and in certain instances aerosol prepared by burning (fume) or aerosol spray compositions can be used.

If the volatile active ingredient gets into the organism by inhalation it has the following advantages:

- it is equivalent to the administration by injection or to the parenteral admininstration,
- it is successful if the per os administration is uncertain due to the function of the enzymes in the digestive canal or if the drug would be changed (some substances are resorbed to a small extent from the gastrointestinal tract), or

- if we want to influence the respiratory system, especially the patological processes of the lung.

The treatment by inhalation can be performed in three forms: the active ingredient to be inhaled, a solution thereof or a cyclodextrin inclusion complex thereof is put into hot water and by utilizing the principle of steam distillation it is transferred to aerosol layer, another possibility is the already mentioned spray where the active ingredient is vapourized with an inert carrier gas under pressure, and according to the third possibility liquid active ingredient is administered to the respiratory system by using the vapourizing principle under clinical conditions and using air of several atmosphere.

The hot water evaporation is the most suitable method to ensure the appropriate amount of water for the respiratory mucous membrane to dissolve the thickened mucous and to enhance the blood supply of the respiratory tract by means of thermal effect and thereby to promote the utilization of the biologically active ingredient.

Upon pouring the volatile oils on hot water (a water temperature of 65 °C is generally sufficient) they evaporate and condense to small drops under cooling after inhalation and thus they get to the bronchus and even to the alveolus, thereby taking their biological effect.

Most of the biologically active ingredients, which can be used as inhalant, are volatile, easily decompose, easily get oxidized, briefly, they get damaged. Due to this fact these substances cannot be tabletted per se and cannot be

applied on solid carrier while reserving their stability.

This problem is solved by the process according to Hungarian Patent Specification No. 182.306. According to this process the volatile active ingredients to be used as inhalants are complexed with cyclodextrins in the form of inclusion complexes, that is they are encapsuled. As a result of this process not only solid active ingredients but liquid and even gas active ingredients can be converted to crystalline powder. The inclusion complexes of cyclodextrin thus prepared can be prepared in the form of satchets or tablets and can be stored without losses of active ingredient within the usual duration of pharmacy trade under the conventional conditions of drug storing. Said compositions can be converted to instant inhalant compositions upon applying them to hot water. The active ingredient included to CD inclusion complex slowly releases in hot water. The disadvantage of this process is that the extent of the release of the active ingredient is not sufficient at the water temperature which ensures the vapour space which can be endured by the human respiratory system. The release of the active ingredient is too slow and a significant amount of it remains in the hot water. The volatile substances are significant in another field apart from the inhalation. They are important during air condition when ensuring the suitable vapour content and volatile substance content of the air. By spreading of modern heating method the air of the apartments and working places gets very dry. This is the source of several deseases of the respiratory tract (drying out of mucous, asthma, etc.). The moisturizing of the

air is practically unavoidable, and it would be advantageous to use natural substances of pleasant odour and partially disinfectant activity in the form of aerosol. When applying the volatile oil CD inclusion complexes prepared according to Hungarian Patent Specification No. 182 306 into suitable mechanical air conditioner and air moisturizing equipment, the whole room can be scented to the desired extent or corresponding to the quality of the used aroma CD inclusion complex. The dosage, the transfer and the storage of the active ingredients can be easily solved.

Practical experiences however showed that in most of the cases the dissociation constant of the cyclodextrin complexes of the volatile active ingredients is too low at the temperature of the application, that means that the release of the complexed active ingredient is slower than desired and its yield is also lower. Though the dissociation of the complex in case of boiling water is rapid and complete, the temperature which can be endured during inhalation for human organism is lower. The steam of 65-80 ^{o}C water can be used as carrier. The complex has to dissociate at room temperature in the air-scenting equipment, and that is the temperature at which the volatile oils have to get into the air space. The release of the active ingredient from the complex can be performed by the following three methods:

a) Enzymatic decomposition of the cyclodextrin forming the inclusion complex. This procedure is too slow and the enzyme has to be added separately.

b) Dissolution of the complex in boiling water (100 ^{o}C) and

its constant boiling. This cannot be used in case of inhalation or air scenting as mentioned before.

c) By increasing the pH of the aqeuous solution. The solubility of cyclodextrin increases somewhat. This accelerates the release of the active ingredient as well.

According to the present invention we get an inhalant composition which releases its active ingredient more rapidly than that in Hungarian Patent Specification No. 182.306 and a higher active ingredient concentration can be achieved in the inhalation space. We experimented in order to prepare a product containing next to the active ingredient included to the inclusion complex a volatile component in a 2-2.5 fold excess in the form of an adsorbeate.

It is rather difficult to elaborate a technique for the prepartion of a product which is reproduceable, standard and contains always the same amount of active ingredient. It has to be considered that the mechanical properties of the obtained mixture complex-adsorbeate are considerably worse than the properties of the complex, i.e. they are sticky, not flowing, decolourizing and their dosage is difficult.

It can be proved by thermal analysis that the volatile substance content of such a product decreases continuously at room temperature and by long storage a product of decreased active ingredient content is obtained. In another series of experiment the pH of the aqueous system was increased as the beta cyclodextrin and crystalline inclusion complexes thereof show a significant increase of solubility in alkaline medium. By adding Na_2CO_3 and Na_2HPO_4 no reproducable increase of

volatility was achieved.

In the course of our further investigations we have surprisingly found that a more complete and rapid release of active ingredient can be achieved from CD volatile substance inclusion complexes if the difference of the stability constant of CD inclusion complex is utilized. It is known that the stability constants of CD inclusion complexes are different. If an inclusion complex is admixed in an aqueous medium with a potent host molecule which is able to form a complex of higher stability with cyclodextrin, then in theory the new host molecule displaces the first molecule.

This principle is used for the determination of the stability constants of cyclodextrin inclusion complexes. Thus for instance beta-cyclodextrin forms a colourless inclusion complex with phenolphthaleine in an alkaline medium the stability contant of which is known. If another molecule displaces part of the phenolphthaleine molecule from the cyclodextrin (this is accompanied by the reappearance of the colour) then from the colour change the stability constant of the cyclodextrin inclusion complex of the new host can be calculated (J.Szejtli: Proceeding of the first International Symposium Cyclodextrins, Reidel, Dordrecht, 1982, J.Szejtli: Cyclodextrins and their Inclusion Complexes, Akadémiai Kiadó, Budapest, 1982). The principle of competition has been used so far only for the mentioned analytical process. The present invention is based on the surprising recognition that this principle can be used for practical preparative purposes which has not been disclosed in the literature.

According to the present invention a potent host molecule is added to the CD-volatile oil composition which is able to form with this cyclodextrin an inclusion complex of considerably higher stability displacing thereby the included volatile active ingredients. Thus the speed and extent of the release of volatile active ingredients included into cyclodextrin in hot water can be accelerated or enhanced by adding a suitable competitor host molecule. The invention was really to find a competitior molecule which could form a more stable inclusion complex with cyclodextrin than the volatile active ingredients included into cyclodextrin. The choice of the compounds was rather great, but the compounds had to meet the following requirements: the competitor host molecule has to be intoxic, easily accessible, solid, non-volatile with water, odourless and it should not react with the components of the inhalant composition. 23 compounds were tested which are shown in Table 1.

Table 1

Tested competitor host molecules

1. Aromatic compounds	benzoic acid, 4-hydroxy-benzoic acid 3-hydroxy-benzoic acid 2-hydroxy-benzoic acid 2-Nipagin-M (4-hydroxy-benzoic acid-methyl ester L-tyrozine L-tryptophan L-phenylalanine
2. Detergents Tween type compounds	Tween 21 poly-oxy-ethylene- Tween 40 sorbitane trioleates, Tween 61 Merck, Darmstadt, Germany Tween 85
Aralkyl-polyglycol-ethers	Arkopal N-090 Arkopal N-050 (Sigma, St. Arkopal N-230 Luis, USA) Triton-X-100 (Röhm et Haas, Phyladelphia, USA)
3. Salts	CTAB = cetyl-trimethyl-ammonium-bromide (Flucka A.G., Switzerland) CPC = cetyl-pyridinium choride (Flucka A.G., Switzerland)
4. Other	cetyl alcohol stearic acid sodium salt of lauryl sulfate glycerol trioleate oleic acid

In Table 1 the release of camphor from beta-cyclodextrin inclusion complex was investigated in a so called inhalation model. In a flask equipped with a thermometer and stirrer 100 cm^3 water is kept at 90 $\pm$ 2 ^oC, and the tested substances are added:

1. 0.5 g free volatile substance (camphor)
2. 5 g camphor-beta-CD complex (active ingredient content 10 %)
3. 5 g camphor beta-CD complex + 0.2 g excipient (substances given in Table 1).

Nitrogen gas is bubbled through the flask with constant speed for 30 minutes. The gas stream is let to a gas washing bottle cooled with ice and containing 50 cm^3 50 % aqueous ethanol solution. The amount of the volatie substance consumed in the trap is determined UV-photometrically. The obtained results are shown in Table II.

Table II

Release of free and complexed camphor in all inhalation model in the present of competitor host molecules

Test sample	Camphor taken up in trap
free camphor	127
camphor β-CD complex	96
camphor β-CD complex + CTAB	115
camphor β-CD complex + CPT	77
camphor β-CD complex + Na-lauryl sulphate	65
camphor β-CD complex + glycerol trioleate	70
camphor β-CD complex + TWEEN 21	92
camphor β-CD complex + TWEEN 40	88
camphor β-CD complex + TWEEN 61	92
camphor β-CD complex + TWEEN 85	102
camphor β-CD complex + Triton-X-100	100
camphor β-CD complex + Arkopal N-030	108
camphor β-CD complex + Arkopal N-050	110
camphor β-CD complex + Arkopal N-230	105
camphor β-CD complex + benzoic acid	168
camphor β-CD complex + 4-OH-benzoic acid	138
camphor β-CD complex + 3-OH-benzoic acid	95
camphor β-CD complex + 2-OH-benzoic acid	140
camphor β-CD complex + Nipagin M	160
camphor β-CD complex + L-tirozine	115
camphor β-CD complex + L-tryptophan	100
camphor β-CD complex + L-phenylalanine	100

As it can be seen the best results are shown by the benzoic acid derivatives. This group was further examined.

1. 10 g camphor β-CD complex (active ingredient content: 10.4 %)
2. camphor β-CD complex + 0.2 g excipient: benzoic acid
   2-hydroxi-benzoic acid (salicylic acid)
   4-hydroxy-benzoic acid
   4-hydroxy-benzoic acid-methyl-ester (Nipagin M)
3. 10 g camphor β-CD complex + 0.2 g excipient + 0.2 g additive
4. 10 g camphor β-CD complex + 10 cm^3 0.1 n sodium hydroxide

The above samples were tested in an inhalation model.

The test results are summarized in Table III.

Table III

Release of complexed camphor in an inhalation model in the presence of benzoic acid and derivatives thereof

Tested sample	Amount of consumed camphor (mg)	%
camphor β-CD complex	325.3	100
camphor β-CD complex + benzoic acid	469.0	144
camphor β-CD complex + 2-hydroxy-benzoic acid (salicylic acid)	387.8	119
camphor β-CD complex + 4-hydroxy-benzoic acid	385.7	119
camphor β-CD complex + 4-hydroxy-benzoic acid + diammonium sulphate	393.4	121
camphor β-CD complex + 4-hydroxy-benzoic acid-methyl ester	378.0	116
camphor β-CD complex + sodium hydroxide	363.2	112

The most intensive release of camphor from the CD-complex could be observed when using benzoic acid as displacing molecule. (The amount of the consumed camphor increased by 44 %.)

It was further investigated how the release of camphor from β-CD complex depends on the amount of the added benzoic acid. Tested sample: 10^9 camphor β-CD complex (active ingredient content 10.4 %). Various amounts of benzoic acid were added and the amount of the consumed camphor was measured in an inhalation model photometrically. The results are shown in Table IV.

Table IV

Release of camphor depending on the amount of benzoic acid

Sample	consumed camphor (mg)	%
complex	269.8	100
complex + 0.2 g benzoic acid	325.3	121
complex + 0.3 g benzoic acid	378.3	140
complex + 0.5 g benzoic acid	416.1	154
complex + 0.7 g benzoic acid	469.1	174
complex + 1 g benzoic acid	542.2	201

On the basis of the results it can be seen that the release of the complexed camphor increases proportionately to the increase of the amount of the benzoic acid. We also wanted to know if benzoic acid or benzoates are more active additives.

Tested sample: 10 g of camphor β-CD complex (active

ingredient content: 10.4 %) to which

1) 0.5 g of benzoic acid

2) 0.5 g of benzoic acid + 0.35 g sodium hydrogen carbonate

are added.

The results measured in the inhalation model are shown in Table V.

Table V

Effect of pH on the ability of benzoic acid to displace camphor

Sample	consumed camphor (mg)	%
Complex	269.8	100
Complex + benzoic acid	416.1	154
Complex + benzoic acid + sodium hydrogen carbonate	314.0	116.4

Table V shows that the benzoate ion is considerably weaker complexing agent (weaker competitor) than the free acid.

The effect of benzoic acid on the release of volatile material was not tested on a camphor model compound but on a definite inhalant composition. The composition

contained

15 g chamomile oil CD complex

25 g mentha oil-CD complex

80 g of eucalyptus oil CD-complex and

45 g of pine oil CD complex

(volatile ingredient content: 10 %).

10 g of this mixture are added to 100 ml of water of a temperature of 90 $\pm$ 2 ^{0}C and to this mixture 0.5 different competitor host molecule was added. The extinction of the absorbing 50 % ethanolic solution measured at 238 nm is shown in Table VI.

Table VI

Release of volatile compounds of the inclusion complex mixture containing the components of the inhalant composition in the inhalation model

Samples	Extinction of ethereal oils taken up in trap at 238 nm	%
Complex	0.700	100
Complex + benzoic acid	1.66 x	237
Complex + Nigapin-M	1.08	154
Complex + 2-OH-benzoic acid	1.25	178
Complex + 3-OH-benzoic acid	1.00	143
Complex + 4-OH-benzoic acid	1.35	193
Complex + L-tyrozine	0.950	135
Complex + L-tryptophan	0.780	111
Complex + CTAB	-	-
Complex + CPC	-	-

x Values higher than 1 are measured extinctions multiplied by dilution.

According to our tests the most suitable compounds for releasing volatile materials from CD complex are benzoic

acid and hydroxy derivatives thereof, and the most preferred compound is the benzoic acid. The precondition of the applicability of benzoic acid and derivatives for inhalation purposes is in case of the used volatile oil complexes that the competitor molecules do not appear in the vapour space at a significant concentration and that they do not get into the respiratory system of the patient at a detrimental amount.

It is known that benzoic acid starts to sublimate in dry state at 120 °C. The volatility of benzoic acid was tested under the conditions of inhalation at 90 ± 2 °C in the previously mentioned inhalation model. The amount of benzoic acid which could be detected in the alcoholic vapour washing bottle together with the active ingredient was measured. The results are shown in Table VII.

Table VII

Amount of benzoic acid getting into the vapour during the model experiment space amount of consumed benzoic acid

Amount of added benzoic acid (mg)	Amount of consumed benzoic acid in mg	Amount of consumed benzoic acid in % of the added amount
300	1.286	0.43
500	2.714	0.5
700	2.857	0.4
1000	3.143	0.3

According to the above results the benzoic acid suggested as additive appears only at a small extent in the inhalation vapour space (0.3-0.5 % of the added amount) and its inspiration in the course of inhalation is substantially negligible.

Under the real conditions cyclodextrin is also present next to the benzoic acid, thus as a consequence of the proved complex formation the amount of the benzoic acid in vapour space is significantly lower than the measured value (substantially cannot be measured).

According to the present invention the inhalant pharmaceutical composition or air scenting composition is characterized by containing a volatile oil-CD inclusion complex and a competitor host molecule as well as conventionally used excipitents. The competitor host molecule forms a complex with CD of higher stability than the volatile active ingredients to be set free. As competitor host molecules the composition contains benzoic acid and/or its hydroxy derivatives such as 2-hydroxy-benzoic acid (salicylic acid) or 4-hydroxy-benzoic acid in 1 to 50 % by weight related to the weight of the volatile active ingredient - CD inclusion complex. The volatile active ingredient - CD inclusion complex contained in our composition can be as follows: camphor CD and/or menthol CD and/or eucalyptus oil CD and/or chamomile oil CD and/or peppermint oil CD and/or pine oil CD and/or beta-ionon CD and/or citral CD and/or lemon oil CD inclusion complex.

Among the volatile active ingredient CD inclusion complexes the beta-CD-inclusion complexes are most preferred. Our present invention further relates to a process to the preparation of an inhalant pharmaceutical composition or air scenting composition containing the active volatile ingredient in the form of CD-inclusion complex by admixing to the volatile active ingredient CD-inclusion complex the competitor host molecule by method known per se. As competitor host molecules benzoic acid and/or its hydroxy derivatives such as 2-hydroxy-benzoic acid (salicylic acid) or 4-hydroxy-benzoic acid can be used in 1 to 50 % by weight related to the volatile active ingredient-CD inclusion complex. As volatile active ingredient-CD-inclusion complex camphor-CD and/or menthol-CD and/or eucalyptus-CD- and/or chamomile oil-CD and/or peppermint oil-CD and/or pine oil CD and/or beta-ionon-CD and/or citral-CD and/or lemon oil-CD inclusion complex can be used. The use of beta-CD-inclusion complexes is most preferred.

According to the process of the invention the volatile active ingredient CD-inclusion complex and the competitor host molecule are admixed with each other in solid state, whereafter the conventionally used filler, diluents and formulating excipients are used to prepare powder or tablet forms of the pharmaceutical and cosmetical compositions.

Further details of the present invention are further illustrated by the following Examples without limiting the scope of the invention to the Examples.

Example 1

Preparation of solid inhalant composition

The composition of the volatile active ingredient corresponds to the composition of Diapulmon oily injectable active ingredient.

Camphor- α-cyclodextrin complex	
(10.2-10.6 % camphor content)	7.317 kg
methol- β-cyclodextrin complex	
(9.9-9.3 % menthol content)	27.134 kg
eucalyptus oil- δ-cyclodextrin complex	
(9.2-9.4 % ethereal oil content)	65.548 kg
benzoic acid	7.2 kg

The mixture is homogenized for 30 minutes in a ball mill. The thus obtained blend is filled to 3 or 5 g satchets and an inhalant powder composition is obtained. The blend is granulated with the conventicnally used additives of an effervescent tablet (sodium hydrogen carbonate + citric acid or tartaric acid and a tablet is obtained of 3 or 6 gramm which can be made effervescent in cold or hot water.

Example 2

We proceed according to Example 1 but benzoic acid is replaced by 4-hydroxy-benzoic acid.

Example 3

We can proceed as disclosed in Example 1 but benzoic acid is replaced by 2-hydroxy-benzoic acid i.e. by salicylic acid.

Example 4

An inhalation powder form containing volatile oils acting on the respiratory system in a cyclodextrin complex.

Composition:

chamomile- β-cyclodextrin complex	
(10-12 % ethereal oil content)	15 kg
peppermint oil- β-cyclodextrin complex	
(10-11 % ethereal oil content)	25 kg
eucalyptus oil- β-cyclodextrin complex	
(10-11 % ethereal oil content)	80 kg
pine oil- β-cyclodextrin complex	
(10-12 % ethereal oil content)	45 kg
benzoic acid	10 kg

The above mixture can be filled to satchets as given in Example 1 or tablets can be prepared according to Example 1.

Example 5

We can proceed as given in Example 4 but benzoic acid is replaced by 4-hydroxy-benzoic acid.

Example 6

We can proceed as given in Example 4 but benzoic acid is replaced by 2-hydroxy-benzoic acid (salicylic acid).

Example 7

An inhalation powder form containing volatile oil acting on the respiratory system.

Composition:

eucalyptus oil-β-cyclodextrin complex (10-11 % volatile material)	89 kg
peppermint oil-β-cyclodextrin complex (10-11 % ethereal oil content)	78.5 kg
chamomile-β-cyclodextrin complex (10-12 % ethereal oil content)	16.7 kg
benzoic acid	5 kg

After homogenizing the above powder mixture the product can be used in a powder form or tablet form as given in Example 1.

Example 8

We can proceed as given in Example 7 but benzoic acid is replaced by 4-hydroxy-benzoic acid.

Example 9

We can proceed as given in Example 7 but benzoic acid is replaced by 2-hydroxy-benzoic acid i.e. salicylic acid.

Example 10

Preparation of air scenting powder form. A beta-ionon-beta-cyclodextrin compolex containing 10-12 % active ingredient is homogenized with tablet additives as given in Example 1 and with 6.6 % by weight of benzoic acid related to the weight of the inclusion complex. The mixture is granulated and finished in the form of effervescent tablets of 6 gramm.

Example 11

We proceed as given in Example 10 but the volatile oil discharging system is citral or natural lemon peal oil--cyclodextrin inlusion complex containing 10-11 % of active ingredient.

Composition:

citral or lemon oil-,S-CD-complex (10-11 % ethereal oil content)	61 kg
tablet additive (polyvinyl pyrrolidone, magnesium-trisilicate, calcium stearate etc.)	39 kg
benzoic acid	7 kg

The above mixture is finished as effervescent tablets of 6 gramm by adding sodium hydrocarbonate and tartaric acid.

C l a i m s :

1. Inhalant pharmaceutical composition or air scenting composition comprising a volatile active ingredient-cyclodextrin inclusion complex and a competitor host molecule as well as conventionally used excipients.

2. Composition as claimed in Claim 1 comprising a competitor host molecule in an amount of 1 to 50 % by weight related to the weight of the volatile active ingredient cyclodextrin inclusion complex.

3. A composition as claimed in any of Claims 1 or 2 comprising as competitor host molecule benzoic acid and/or its hydroxy derivatives, preferably 2-hydroxy-benzoic acid or 4-hydroxy-benzoic acid.

4. A composition as claimed in ary of Claims 1 to 3 comprising as a volatile active ingredient cyclodextrin inclusion complex, camphor cyclodextrin and/or menthol cyclodextrin and/or pine oil cyclodextrin and/or beta-ionon-cyclodextrin and/or citral cyclodextrin and/or lemon oil cyclodextrin and/or eucalyptus oil cyclodextrin and/or peppermint oil cyclodextrin and/or chamomile oil cyclodextrin inclusion complex, preferably beta-cyclodextrin inclusion complex.

5. Process for the preparation of an inhalant pharmaceutical composition or air scenting composition comprising adding a competitor host molecule to the volatile active ingredient cyclodextrin inclusion complex and finishing the mixture as a usual pharmaceutical or cosmetical composition.

6. A process according to Claim 5 which comprises using the competitor host molecule in 1 to 50 % by weight related to the volatile active ingredient cyclodextrin inclusion complex.

7. A process according to any of Claims 5 or 6 which comprises using as a competitor host molecule benzoic acid and/or hydroxy derivatives thereof, such as 2-hydroxy-benzoic acid or 4-hydroxy-benzoic acid.

8. A process according to any of Claims 5 to 7 which comprises using as volatile active ingredient cyclodextrin inclusion complex camphor-cyclodextrin and/or menthol-cyclodextrin and/or eucalyptus oil-cyclodextrin and/or chamomile oil-cyclodextrin and/or peppermint oil-cyclodextrin and/or pine oil-cyclodextrin and/or beta-ionon-cyclodextrin and/or citral cyclodextrin and/or lemon oil cyclodextrin inclusion complex, preferably beta-cyclodextrin inclusion complex.

9. A process according to any of Claims 5 to 8 which comprises admixing the volatile active ingredient cyclo-

dextrin inclusion complex with benzoic acid and/or hydroxy derivatives thereof in solid state.

10. A process according to any of Claims 5 to 9 which comprises preparing the inhalant or air scenting composition by using the conventionally used filling agents, diluants and formulating excipients and preparing powder or tablet forms.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 88/00025

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

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II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[4]	A 61 K 9/00,7/00,31/00; A 61 L 9/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P,X	EP, A2, 0 233 615 (SENJU PHARMACEUTICAL CO., LTD.) 26 August 1987 (26.08.87), see claims 1,4; example 1; page 3, lines 1-12.	(1)
X	GB, A, 1 450 809 (TEIJIN LIMITED) 29 September 1976 (29.09.76), see claims 13, 17,19-25; examples 1,2.	(1,4,5,8,10)
X	GB, A, 2 173 400 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 15 October 1986 (15.10.86), see claims 1,2,4-7,9-12; examples 2,8,9; page 9, lines 24-31.	(1,3,4,5,7-10)
Y	HU, A, 182 306 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 31 October 1986 ((31.10.86), see claim 1; examples 6,7.	(1,4,5,8,10)
Y	GB, A, 679 573 (THE MENTHOLATUM COMPANY LIMITED) 17 September 1952 (17.09.52), see claims 1,2; example.	(1,4,5,8,10)

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 July 1988 (05.07.88)	12 July 1988 (12.07.88)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	Pippan

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	GB, A, 1 515 630 (S.C.JOHNSON AND SON INC.) 28 June 1978 (28.06.78), see claims 1,4,5, 7,8; page 2, lines 38-43; page 3, lines 3-8; example 1.	(1,4,5,8-10)
Y	EP, A1, 0 013 688 (KYOSHIN CO., LTD.) 06 August 1980 (06.08.80), see claims 1,2,4, 5; examples 1,2; page 3, line 32 - page 4, line 2.	(1,4,5,8-10)
A	US, A, 4 247 535 (A.J.LEWIS, S. BERNSTEIN) 27 January 1981 (27.01.81), see example 8.	(1,2,5,6)
A	EP, A1, 0 056 995 (THE WELLCOME FOUNDATION LIMITED) 04 August 1982 (04.08.82), see example 6c; claims 9,10; page 5, lines 1-20; page 6, lines 7-13.	(1,3-5,7-10)
A	Journal of Pharmaceutical Sciences, vol. 52, published 1963, J. COHEN, J.L. LACH "Interaction of Pharmaceuticals with Schardinger Dextrins I", see pages 132-136; especially page 133, last passage - page 134, first passage, conclusion.	(1,3,5,7,9)

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Annex to the International Search Report on International Patent Application No. PCT/HU 88/00025

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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